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Award Number: W81XWH-08-1-0755

TITLE: Importance of Virtual Reality to a Controlled Stimulus

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REPORT DATE: October 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-10-2011	Annual	25 Sep 2010 - 24 Sep 2011

4. TITLE AND SUBTITLE
Importance of Virtual Reality to a Controlled Stimulus

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-1-0755

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Geneva Foundation
Lakewood, WA 96496

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a follow up to two projects, funded by the Office of Naval Research, which demonstrated that Virtual Reality (VR) Exposure Therapy was safe for the treatment of combat PTSD Disorder, and that it worked better than treatment as usual. In this study, we are attempting to discover if the Virtual Realty is actually the active component of the treatment. Participants with PTSD are randomized to receive the same treatment that was successful in the previous projects, or the same treatment in which a simple, still computer image replaces the VR. At the initial onset of the project we were delayed by 6 months for administrative reasons. The project has since that time consistently been 6 months behind, but is otherwise going as anticipated. In the last year, we have continued to recruit, assess, and treat individuals with combat related PTSD. We have completed treatment of a little over half the targeted number of subjects, and within the next 10 weeks, if currently enrolled subjects complete treatment, will reach 75% of our target enrollment. Preliminary analysis from current subjects is showing that the use of the VR does not significantly improve outcomes immediately after treatment. However, at 3-month follow up, subjects who had received VR had greater treatment gains than those in the control condition.

15. SUBJECT TERMS
Post Traumatic Stress Disorder, Anxiety, Depression, Virtual Reality, Psychotherapy, Exposure Therapy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION: This study is intended to determine if the Virtual Reality (VR) simulator used in Virtual Reality Exposure Therapy (VRET) is the active component when using the technique to treat combat-related PTSD. It is a multi-site, randomized, single blind comparison of VRET versus a control condition that uses all the same components of therapy, except that a single, still computer image is used to focus a subject's attention rather than having him/her use a full, VR simulator. The VRET is conducted in the same fashion as has been previously used to treat combat PTSD. Subjects receive therapy for up to twice a week therapy for ten weeks. Subjects are assessed by independent, blinded raters before and after treatment, and three months later to determine long-term follow up. Success is determined by showing improvements on the Clinician Administered PTSD Scale (CAPS). The study was designed to complete treatment of 80 subjects (40 active and 40 controls) over the course of 4 years. A fifty percent dropout rate was anticipated. The study was to be completed at two military facilities, Naval Medical Center San Diego, and Marine Corps Base Camp Pendleton. We are attempting to add a third site, at Naval Hospital Yokosuka, Japan. Naval Hospital Twenty Nine Palms has recently reached out to us to potentially be added as a fourth site, but we are unsure if we will be able to support this. Because of funding cuts to the original budget, the study is dependent on including volunteer research therapists and research assistants who work on the project without cost to the grant. At the last annual review, we reported that we had successfully set up the study, and were training therapists, recruiting and treating subjects, and gathering data. At that point, no significant results had yet been found.

BODY:

During the last year, the study has continued without significant difficulties. We recently completed our annual IRB review, and with it an annual review of current findings. This preliminary analysis indicates that VRET is not resulting in significantly greater improvements in PTSD symptoms when compared to the same therapy without the use of the 3-D simulator. However, these same preliminary results did find a statistically significant advantage in PTSD symptom reduction when examining scores at the 3 month follow up point.

Currently, we have six therapists actively treating patients, and five simulators where treatment can be conducted. The therapists include the PI, two part-time research psychologists paid for by the grant, and three volunteer therapists. At various points we have been joined by four other volunteer therapists, but due to turnover among military staff, voluntary therapist have come and gone. Although training so many therapists has meant occasional delays in the study, we believe it will help the project overall, both because it gives a more representative sample of how subjects might respond to the method, and, if the project is successful, it means that there are already providers who could use the technique, and train others, should the VRET method prove superior to traditional treatment. Therapists must have prior experience in traditional exposure therapy, complete IRB research requirements, and complete a supervised "training case" in VRET before we would include data from subjects treated by that provider. With the therapists we currently have, we are currently able to treat up to 9 patients at a time. We need to maintain 4 subjects in treatment at all times to maintain project goals. All research therapists also participate in a weekly supervision and monitoring meeting (in person or by video conference) in which protocol adherence is maintained.

So far, ninety-one subjects have given informed consent to be assessed for the study. Sixteen of these did not meet study criteria and were excluded. Five subjects were treated by a first-time therapist, and therefore were considered "training cases", with data excluded from analysis. Nineteen subjects elected not to enter treatment (dropped out prior to randomization). Four subjects (two active, and two controls) dropped from the study after enrollment. One of these four was due to an adverse event (becoming suicidal during treatment). The other three electively left the program. Thirty-nine subjects completed treatment and a post-treatment

assessment. One of these subjects will likely need to be excluded because it was discovered that he was undergoing another research treatment at the same time as the VRET. All but one of the subjects who completed received a minimum of 6 treatment sessions, the minimum number we would expect to be needed to see an effect from treatment. Nine subjects are currently in treatment. Twenty one subjects have contributed long-term (3 month +) follow up data**.** Recruitment is ongoing.

We completed preliminary safety and efficacy review in preparation for the annual IRB review. Both groups of subjects experienced statistically and clinically significant improvements over the course of treatment. Average improvement was 26% (21 points) in controls, and 18% (16 points) in the Active VR condition immediately following treatment. This was not a statistically significant difference between two treatment conditions. Of controls, 50% had experienced a clinically meaningful improvement (>30% improvement), and 38% of those treated in the active condition had experienced a similarly, clinically-significant change (not a statistically significant difference. Of note, in the single group study that preceded this one, 75% of patients had experienced clinically significant improvements at post-treatment. Also, unlike the previous study, we found a small number of subjects (n=3 per group), both in active and control conditions, who got significantly worse (>20% increase in symptoms) during the course of treatment. We are not yet sure of the reasons for these differences.

At the three month follow up, we found that some subjects who had improved in the active or control treatment continued to improve in the interval. We also found that many subjects, particularly in the control condition, found that their symptoms returned, or even worsened during the follow up interval. However, with only one exception, we found that subjects who failed to respond initial treatment (either VRET or control) did not improve in the follow up interval, regardless of what additional treatment was offered.

At three month follow up, subjects who had received the control treatment showed no statistically significant improvements compared to their baseline assessment. This is surprising given that the control treatment is essentially traditional Prolonged Exposure therapy, which is normally thought of as the gold standard for treating PTSD. The lack of overall change, however, may be misleading, as it consisted both of patients who were now worse than when initially assessed, those who had relapse of their symptoms, and those who had maintained and furthered their treatment gains. In fact, 27% of control subjects marked still had PTSD symptom severity scores that were at least 30% lower than they were before treatment.

In contrast to the subjects in the control condition, subjects who had received VRET maintained their gains during the 3-month follow up interval. VRET subjects were, showed a 42% (31 point) drop in PTSD symptoms compared to their baseline. Sixty percent of subjects now showed a clinically significant improvement (>30% drop) compared to baseline. This was not statistically different than scores immediately post-treatment. The percent and point improvement were both significantly greater ($p<0.05$) in those who had received VRET than in controls.

In summary, preliminary results indicate that the use of VR in exposure therapy does not appear to improve the likelihood or magnetite of improvements in PTSD. However, subjects who are treated with VR appear to be more likely to maintain and improve on their therapy gains after treatment than those who went through exposure therapy without the VR.

These results have not yet been presented, and no new publications or presentations have occurred in the last year. We anticipate putting our preliminary findings forward as a meeting abstract within the next year, but will hold off on journal publication until the complete sample size is gathered.

We have all aspects in place to continue to gather data for the full sample size. Safety and IRB review has been completed for the year, and we intend to continue on with our current methods. Our two research sites, Naval Medical Center San Diego, and Marine Corp Base Camp

Pendleton are functioning according to plan. We have been attempting to add U.S. Fleet Activities Base Sasebo, Japan, as a third research site for the project, but the tsunami in Japan delayed this moving forward. We are hoping to get this site added within the next year, however and will provide a letter of support once obtained. Naval Hospital Twenty Nine Palms has also reached out to us to be another potential research site, manned with volunteer psychologists and research techs, but we are unsure if we will be able to support this fourth site.

Only one item from the statement of work is relevant to the current study period:
Task 2: Month 7 to month 42: Recruit and enroll approximately 8 patients per treatment period, with the expectation that 4 of these will enter VRET or CET treatment phases, and be eligible for intention to treat analysis.

In the initial fiscal year, we started this phase six months late. We continue to be approximately six months behind our overall goals in terms of recruiting and treatment subjects in the protocol. Our current enrollment and treatment rate slightly exceeds the 4 subjects at a time, anticipated, but not at great enough a rate to fully make up for the initial starting delay.

KEY RESEARCH ACCOMPLISHMENTS:

- Key personnel and procedures in place to conduct and test Virtual Reality Exposure Therapy versus the control condition
- Annual safety and efficacy review was conducted, which showed that subjects are improving in both treatments. Preliminary analysis indicates that the addition of Virtual Reality does not improve initial outcomes in prolonged exposure, but that the long term outcomes appear to be better when Virtual Reality is used.
- All elements in place to continue to treat subjects and gather data for the following year.

REPORTABLE OUTCOMES:

In the last year, we have not published any results nor made any presentations at research meetings. However, an abstract was accepted to present the preliminary findings of the study at the 2012 meeting of the American Psychiatric Association.

This project has been highlighted as part of several VIP visits to Naval Medical Center San Diego, and has become one of the standard highlights for VIP tours of the medical center. This included presentations to the new commanding admiral for NMCSD and Navy Medicine West, Rear Admiral Faison, and the new Executive Steering Committee for Navy Medicine West.

Five Virtual Reality simulators have been established in military mental health clinics, and a sixth is available to use in Japan if and when that site is opened. Twenty nine therapists from military clinics have been given basic instruction in how to conduct virtual reality therapy, and nine therapists have completed training to the point that they could function as therapists on the grant.

CONCLUSION: Preliminary findings confirm previous reports that VRET is a safe and effective treatment for combat-related PTSD. Preliminary results suggest that VRET may offer more lasting gains than prolonged exposure done without benefit of the full simulator, but this will need to be confirmed by completing the full study.

REFERENCES: Not applicable.

APPENDICES: None

SUPPORTING DATA:

Percent improvement in PTSD symptoms as assessed by the CAPS, before and immediately after treatment, and before and 3-months after treatment is complete.